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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,147	10/05/2000	Tomoki Todo	066683/0188B	7711

7590 12/19/2001

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EXAMINER
BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
1632	5

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/679,147	Applicant(s) TODO ET AL.
	Examiner Anne M Beckerleg	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 15 and 27 are objected to because of the following informalities: parts of claims 15 and 27 on pages 10 and 11 respectively are hidden by punch holes. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the growth of a solid neuroblastoma by intratumoral injection of a defective Herpes Simplex Virus (HSV) vector encoding a soluble B7-1-Ig fusion protein, does not reasonably provide enablement for the treatment of any type of tumor in a mammal by administering any vector encoding any soluble co-stimulatory factor using any route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses the treatment of tumors in vivo by the generation of anti-tumor immune responses following the administration of vector encoding a soluble co-stimulatory factor. The specification discloses that preferred co-stimulatory factors include membrane bound proteins such as CD40, the B7 family, LFA-3, CD2, and ICAM-1. In addition, the specification teaches that a vector encoding an immunomodulator such as a cytokine or chemokine can be co-administered to increase anti-tumor immune responses. The specification provides a working example of the invention which demonstrates that the intratumoral injection of a defective HSV vector encoding soluble B7-1-Ig to a subcutaneous neuroblastoma in mice results in decreased growth of the tumor compared to vector controls. The working examples further demonstrate that the mechanism of B7-1-Ig in reducing tumor growth is based on immune responses since tumors in immunodeficient nude mice were not affected by B7-1-Ig expression.

The specification does not provide an enabling disclosure for making or using a vector encoding a soluble co-stimulatory molecule other than B7-1-Ig. The specification discloses that membrane-bound molecules with co-stimulatory ability, including CD40, CD48, CD72, and CD2, can be modified to a soluble form for use in the instant invention. While the specification provides some guidance for making a fusion protein encoding the B7-1 extracellular domain operably linked to the Fc portion of human IgG1, the specification provides no guidance for making any other soluble co-stimulatory molecule. The specification fails to teach or describe how other membrane bound co-stimulatory molecules can be modified to generate a soluble form of the protein. The specification further does not provide sufficient guidance for making a soluble

co-stimulatory molecule with two extracellular domains or making a soluble co-stimulatory molecule which is a dimer. In addition, the specification fails to teach the level of soluble co-stimulatory gene expression which correlates with any effect on tumor growth for any and all co-stimulatory molecules and any and all tumors. The co-stimulatory molecules listed in the specification all have different ligands and mediate or transduce different signals in T cells such that a nexus cannot be drawn between the applicant's working example using B7-1-Ig and other substantially different co-stimulatory molecules. The applicant is reminded that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Furthermore, the Federal Circuit has stated that:

..a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

The specification further does not provide an enabling disclosure for the targeted delivery of any vector to any type of tumor or "tumor-related " cell in vivo. The claims as written are extremely broad and read on the administration of vectors encoding a soluble co-stimulatory

molecule using any route of delivery. The claims also recite the use of vectors that are targeted to tumors. However, the specification provides no guidance for any vector that is capable of specifically targeting any tumor type, or teach any method of modifying any currently known vector in order to target any type of cell *in vivo*. The specification also fails to provide sufficient guidance for the parameters affecting the targeted delivery of any and all viruses to any cell type *in vivo*, such as route and site of administration, dosage of vector, etc, other than direct intratumoral injection. At the time of filing, the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). Thus, in view of the art recognized unpredictability of targeting vector to specific cell types *in vivo*, the lack of guidance for making and administering any vector capable of targeting any cell type, the limitation of the working examples to intratumoral injection of vectors, and the breadth of the

claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The specification also does not provide an enabling disclosure for using any vector/promoter combination to express therapeutic amounts of B7-1-Ig *in vivo*. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the

latter issue, Verma states that, "the search for such combinations is a case of trail and error for a given cell type" (Verma, (1997) Nature, 389, page 240).

In addition, cancer immunotherapy is further complicated by the fact that in order for tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen. At the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would prevent from being recognized by the tumor specific cytotoxic T cells. The art at the time of filing also specifically recognized the difficulties in generating therapeutic anti-tumor immune responses using gene therapy. Orkin et al. states in regards to the immunotherapy of cancer that, " although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans", and that, " [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) page 1, paragraph 3, page 6, paragraph 6).

Thus, based on the art recognized unpredictability of achieving therapeutic levels of gene expression using currently available vectors at the time of filing, the unpredictability of treating cancer using immunotherapy, the art recognized unpredictability of targeting vectors to specific

cell types *in vivo*, the lack of guidance for making and using nucleic acids encoding soluble co-stimulatory factors other than B7-1-Ig, the heterogeneity of tumors in regards to their ability to express antigen and stimulate T cells, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to treat any and all tumors by administering any vector encoding any soluble co-stimulatory factor using any route of administration.

. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22, and 24-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "tumor-related" cells. It is unclear what types of cells would be considered "tumor-related". Further, the specification does not provide sufficient guidance for this term such that the metes and bounds of the claim can be determined. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1, 7-11, 17-25, and 28-32 are rejected under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 6,310,045, 10/30/01, hereafter referred to as Barber et al. The applicant claims methods of activating or enhancing a T-cell response in a patient with a tumor comprising administering a vector encoding a soluble costimulatory factor. The applicant further claims said methods wherein the vector is a retroviral vector or a non-viral vector, said method wherein the vector is administered with a liposome carrier, or wherein said administering further comprises the administration of a nucleic acid sequence encoding an immune modulator such as a cytokine.

Barber et al. teaches methods of inhibiting the growth of a solid tumor by direct intratumoral administration of a retroviral vector encoding IL-2 (Barber et al., column 55, claim 1). Barber et al. further teaches said method wherein a retroviral vector encoding the cytokine IFN-gamma is also administered to the tumor (Barber et al., columns 55, claim 2). Barber et al. also teaches that the IL-2 inhibits tumor growth by stimulating a cytotoxic immune response (Barber et al., columns 1-2, bridging paragraph). It is also noted that IL-2 was well characterized at the time of filing, and was recognized by the art as a co-stimulatory factor based on its ability to act as a second signal for T cell activation. In addition, Barber et al. teaches that other vectors

systems can be used to deliver IL-2 directly to a tumor, including plasmid DNA, DNA conjugated to liposomes, vaccinia virus, adenovirus, or adeno-associated virus (Barber et al., columns 10-11). Thus, by teaching all the elements of the claims, Barber et al. anticipates the instant invention.

Claims 23 and 39 are rejected under 35 U.S.C. 102 (b) as being anticipated by Hollenbaugh et al. (1992) EMBO J., Vol. 11 (12), 4313-4321. The applicant claims a pharmaceutical composition comprising a vector encoding a soluble co-stimulatory factor and a pharmaceutically accepted carrier. In regards to the intended use of the compound of this composition as a "pharmaceutical" composition, it is noted that the intended use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Hollenbaugh et al. teaches the construction of a plasmid DNA encoding a soluble recombinant form of gp39, the ligand for CD40, which is capable of transfecting mammalian cells (Hollenbaugh et al., page 4319-4320). Thus, by teaching all the elements of the claims, Hollenbaugh et al. anticipates the instant invention.

Claims 23 and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Sturmhoefel et al. (10/1/99) Canc. Res., Vol. 59(19), 4964-4972. The applicant claims a pharmaceutical composition comprising a vector encoding a soluble co-stimulatory factor and a pharmaceutically accepted carrier. In regards to the intended use of the compound of this composition as a "pharmaceutical" composition, it is noted that the intended use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Sturmhoefel et al. teaches the construction of a plasmid vector encoding a soluble B7-1-Ig or B7-2-Ig fusion protein capable of transfecting mammalian cells (Sturmhoefel et al., pages 4964-4965). Thus, by teaching all the elements of the claims, Hollenbaugh et al. anticipates the instant invention.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be

reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER